

## PATENT COOPERATION TREATY

PCT

## NOTIFICATION OF ELECTION

(PCT Rule 61.2)

From the INTERNATIONAL BUREAU

To:

Assistant Commissioner for Patents  
 United States Patent and Trademark  
 Office  
 Box PCT  
 Washington, D.C. 20231  
 ETATS-UNIS D'AMERIQUE

in its capacity as elected Office

<b>Date of mailing (day/month/year)</b> 17 August 2000 (17.08.00)	
<b>International application No.</b> PCT/US99/30900	<b>Applicant's or agent's file reference</b> REG 670 -A-PCT
<b>International filing date (day/month/year)</b> 23 December 1999 (23.12.99)	<b>Priority date (day/month/year)</b> 23 December 1998 (23.12.98)
<b>Applicant</b> DAVIS, Samuel, J. et al	

1. The designated Office is hereby notified of its election made:

☒ in the demand filed with the International Preliminary Examining Authority on:

23 June 2000 (23.06.00)

☐ in a notice effecting later election filed with the International Bureau on:2. The election ☒ was☐ was not

made before the expiration of 19 months from the priority date or, where Rule 32 applies, within the time limit under Rule 32.2(b).

<b>The International Bureau of WIPO</b> 34, chemin des Colombettes 1211 Geneva 20, Switzerland  Facsimile No.: (41-22) 740.14.35	<b>Authorized officer</b>  A. Karkachi  Telephone No.: (41-22) 338.83.38
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# PATENT COOPERATION TREATY

# PCT

## INTERNATIONAL SEARCH REPORT

(PCT Article 18 and Rules 43 and 44)

Applicant's or agent's file reference <b>REG 670 -A-PCT</b>	<b>FOR FURTHER ACTION</b> <small>see Notification of Transmittal of International Search Report (Form PCT/ISA/220) as well as, where applicable, item 5 below.</small>	
International application No. <b>PCT/US 99/ 30900</b>	International filing date (day/month/year) <b>23/12/1999</b>	(Earliest) Priority Date (day/month/year) <b>23/12/1998</b>
Applicant  <b>REGENERON PHARMACEUTICALS, INC. et al.</b>		

This International Search Report has been prepared by this International Searching Authority and is transmitted to the applicant according to Article 18. A copy is being transmitted to the International Bureau.

This International Search Report consists of a total of 5 sheets.

☒ It is also accompanied by a copy of each prior art document cited in this report.

**1. Basis of the report**

a. With regard to the **language**, the international search was carried out on the basis of the international application in the language in which it was filed, unless otherwise indicated under this item.

☐ the international search was carried out on the basis of a translation of the international application furnished to this Authority (Rule 23.1(b)).

b. With regard to any **nucleotide and/or amino acid sequence** disclosed in the international application, the international search was carried out on the basis of the sequence listing :

☐ contained in the international application in written form.

☐ filed together with the international application in computer readable form.

☒ furnished subsequently to this Authority in written form.

☒ furnished subsequently to this Authority in computer readable form.

☒ the statement that the subsequently furnished written sequence listing does not go beyond the disclosure in the international application as filed has been furnished.

☒ the statement that the information recorded in computer readable form is identical to the written sequence listing has been furnished

2. ☐ **Certain claims were found unsearchable** (See Box I).

3. ☐ **Unity of invention is lacking** (see Box II).

4. With regard to the **title**,

☒ the text is approved as submitted by the applicant.

☐ the text has been established by this Authority to read as follows:

5. With regard to the **abstract**,

☒ the text is approved as submitted by the applicant.

☐ the text has been established, according to Rule 38.2(b), by this Authority as it appears in Box III. The applicant may, within one month from the date of mailing of this international search report, submit comments to this Authority.

6. The figure of the **drawings** to be published with the abstract is Figure No.

☐ as suggested by the applicant.

☐ because the applicant failed to suggest a figure.

☐ because this figure better characterizes the invention.

☐ None of the figures.

## INTERNATIONAL SEARCH REPORT

International Application No.

US 99/30900

## A. CLASSIFICATION OF SUBJECT MATTER

IPC 7 C12N15/12 C12N15/62 C12N5/10 C12N1/21 C07K14/515  
C07K14/52

According to International Patent Classification (IPC) or to both national classification and IPC

## B. FIELDS SEARCHED

Minimum documentation searched (classification system followed by classification symbols)

IPC 7 C12N C07K

Documentation searched other than minimum documentation to the extent that such documents are included in the fields searched

Electronic data base consulted during the international search (name of data base and, where practical, search terms used)

## C. DOCUMENTS CONSIDERED TO BE RELEVANT

Category *	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
X	WO 96 37621 A (MORPHOSYS PROTEINOPTIMIERUNG ;PACK PETER (DE); HOESS ADOLF (DE)) 28 November 1996 (1996-11-28) abstract page 1, line 12 - line 15 page 2, line 4 - line 9 page 14, line 6 - line 11 page 16, line 29 - line 34 figure 1A	1-5, 12-22
Y A	---	8-11 6,7
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☒ Further documents are listed in the continuation of box C.☒ Patent family members are listed in annex.

## \* Special categories of cited documents:

"A" document defining the general state of the art which is not considered to be of particular relevance

"E" earlier document but published on or after the international filing date

"L" document which may throw doubts on priority claim(s) or which is cited to establish the publication date of another citation or other special reason (as specified)

"O" document referring to an oral disclosure, use, exhibition or other means

"P" document published prior to the international filing date but later than the priority date claimed

"T" later document published after the international filing date or priority date and not in conflict with the application but cited to understand the principle or theory underlying the invention

"X" document of particular relevance; the claimed invention cannot be considered novel or cannot be considered to involve an inventive step when the document is taken alone

"Y" document of particular relevance; the claimed invention cannot be considered to involve an inventive step when the document is combined with one or more other such documents, such combination being obvious to a person skilled in the art.

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Date of the actual completion of the international search

22 May 2000

Date of mailing of the international search report

09/06/2000

Name and mailing address of the ISA

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Authorized officer

Galli, I

## INTERNATIONAL SEARCH REPORT

International Application No

/US 99/30900

## C.(Continuation) DOCUMENTS CONSIDERED TO BE RELEVANT

Category *	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
X	WO 92 03569 A (SANGSTAT MEDICAL CORP) 5 March 1992 (1992-03-05) abstract page 1 -page 3 page 19, line 14 - line 23	23-26, 29, 32-41
Y A	---	30 27, 28
Y	WO 95 27060 A (REGENERON PHARMA) 12 October 1995 (1995-10-12) cited in the application abstract page 23, line 21 -page 24, line 8 claims 4, 8	8-11, 30
A	EP 0 816 510 A (TORAY RESEARCH CENTER INC ;TORAY INDUSTRIES (JP)) 7 January 1998 (1998-01-07) abstract	1-22
A	DAVIS S. ET AL.: "Isolation of Angiopoietin-1, a ligand for the TIE2 receptor, by secretion-trap expression cloning" CELL, vol. 87, 27 December 1996 (1996-12-27), pages 1161-1169, XP002138354 cited in the application the whole document	6, 7, 27, 28
A	MAISONPIERRE P.C. ET AL.: "Angiopoietin-2, a natural antagonist for Tie2 that disrupts in vivo angiogenesis." SCIENCE, vol. 277, 4 July 1997 (1997-07-04), pages 55-60, XP002138355 cited in the application the whole document	6, 7, 27, 28
A	TOURNAY C. ET AL.: "Uptake of recombinant myeloperoxidase, free or fused to Fc-gamma, by macrophages enhances killing activity towards micro-organisms" DNA CELL BIOLOGY, vol. 15, no. 8, 1996, pages 617-624, XP000907279 abstract page 618	21, 40

# INTERNATIONAL SEARCH REPORT

Information on patent family members

International Application No

US 99/30900

Patent document cited in search report		Publication date	Patent family member(s)		Publication date
W0 9637621	A	28-11-1996	CA	2222055 A	28-11-1996
			EP	0827544 A	11-03-1998
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EP 0816510	A	07-01-1998	CA	2213512 A	03-07-1997
			W0	9723639 A	03-07-1997

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## INTERNATIONAL APPLICATION PUBLISHED UNDER THE PATENT COOPERATION TREATY (PCT)

<b>(51) International Patent Classification <sup>7</sup> :</b> <b>C12N 15/12, 15/62, 5/10, 1/21, C07K</b> <b>14/515, 14/52</b>		<b>A1</b>	<b>(11) International Publication Number:</b> <b>WO 00/37642</b>
			<b>(43) International Publication Date:</b> 29 June 2000 (29.06.00)
<b>(21) International Application Number:</b> PCT/US99/30900 <b>(22) International Filing Date:</b> 23 December 1999 (23.12.99) <b>(30) Priority Data:</b> 60/113,387 23 December 1998 (23.12.98) US <b>(71) Applicant (for all designated States except US):</b> REGENERON PHARMACEUTICALS, INC. [US/US]; 777 Old Saw Mill River Road, Tarrytown, NY 10591-6707 (US). <b>(72) Inventors; and</b> <b>(75) Inventors/Applicants (for US only):</b> DAVIS, Samuel, J. [US/US]; 332 W. 88th Street, #B2, New York, NY 10024 (US). GALE, Nicholas, W. [US/US]; Apartment 46V, 177 White Plains Road, Tarrytown, NY 10591 (US). YANCOPOULOS, George, D. [US/US]; 1519 Baptist Church Road, Yorktown Heights, NY 10598 (US). STAHL, Neil [US/US]; RD # 10, Kent Shore Drive, Carmel, NY 10512 (US). <b>(74) Agents:</b> PALLADINO, Linda, O.; Regeneron Pharmaceuticals, Inc., 777 Old Saw Mill River Road, Tarrytown, NY 10591 (US) et al.			<b>(81) Designated States:</b> AE, AL, AM, AT, AU, AZ, BA, BB, BG, BR, BY, CA, CH, CN, CU, CZ, DE, DK, EE, ES, FI, GB, GD, GE, GH, GM, HR, HU, ID, IL, IN, IS, JP, KE, KG, KP, KR, KZ, LC, LK, LR, LS, LT, LU, LV, MD, MG, MK, MN, MW, MX, NO, NZ, PL, PT, RO, RU, SD, SE, SG, SI, SK, SL, TJ, TM, TR, TT, UA, UG, US, UZ, VN, YU, ZA, ZW, ARIPO patent (GH, GM, KE, LS, MW, SD, SL, SZ, TZ, UG, ZW), Eurasian patent (AM, AZ, BY, KG, KZ, MD, RU, TJ, TM), European patent (AT, BE, CH, CY, DE, DK, ES, FI, FR, GB, GR, IE, IT, LU, MC, NL, PT, SE), OAPI patent (BF, BJ, CF, CG, CI, CM, GA, GN, GW, ML, MR, NE, SN, TD, TG).  <b>Published</b> <i>With international search report.</i> <i>Before the expiration of the time limit for amending the claims and to be republished in the event of the receipt of amendments.</i>

**(54) Title:** METHOD OF ENHANCING THE BIOLOGICAL ACTIVITY OF LIGANDS**(57) Abstract**

Novel fusion polypeptide ligands that bind Eph family receptors or the Tie-2 receptor are identified, and methods for making the fusion polypeptide ligands in biologically active form are described. Nucleic acids encoding these novel fusion polypeptide ligands enable production of the fusion polypeptide ligands. The method of making the nucleic acids and the fusion polypeptide ligands is broadly applicable to the production of polypeptide ligands in general, resulting in improved affinity and/or increased activity of the ligand when compared to its native form.

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